IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

7-2000
# 12
Appeal Brief

Appellant: M. Rigdon Lentz

Serial No.: 09/083,307 Art Unit: 3762

Filed: May 22, 1998 Examiner: W. Noggle

For: *METHOD AND COMPOSITIONS FOR TREATMENT OF CANCERS*

Board of Patent Appeals and Interferences
United States Patent and Trademark Office
Washington, D.C. 20231

**APPEAL BRIEF**

Dear Sir:

This is an appeal from the Office Action mailed January 4, 2000, finally rejecting claims 1-23, and maintained in the Advisory Action mailed April 24, 2000, in the above-identified patent application. A Notice of Appeal was mailed May 12, 2000. A check in the amount of $150.00 for the filing of this Appeal Brief is enclosed.

## (1) REAL PARTY IN INTEREST

The real party in interest of this application is M. Rigdon Lentz.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant or the undersigned which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 1-23 are pending, rejected, and on appeal. The text of each claim on appeal, as pending, is set forth in the Appendix to this Appeal Brief.

## (4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed September 23, 1999.

## (5) SUMMARY OF THE INVENTION

The invention is the discovery that one can use a filter to selectively remove molecules of less than 120,000 daltons from the blood of a patient and induce remission in a cancer or other type of chronic disease, and that this process, in combination with certain adjuvant therapies, can not only induce a remission, but maintain the patient in remission. [Page 2, line 27 to page 3, line 27]. The filtration process removes material which is apparently produced by the cancer to prevent the patient from killing the tumors. The adjunct therapy is typically treatment with an anti-angiogenic compound, treatment with one or more cytokines, or a procoagulant compound, although it may be more conventional chemotherapy or radiation (page 3, lines 7-17).

The examples demonstrate that the method was effective in treating cancer patients. The first example at pages 12-13, was a lung cancer patient who had failed conventional chemotherapy. Filtration alone reduced the tumor size and number. The second example at page 13 described a woman with metastatic breast cancer who had failed radiation and conventional chemotherapy. Filtration was used to enhance immune attack on the tumors (leading to inflammation, see page 13, lines 12-16), then thalidomide, an anti-angiogenic compound, used to further resolve the tumors. Example three at pages 13-14 was a patient with metastatic melanoma who was treated initially with filtration to induce tumor inflammation, then treated with thalidomide to induce remission. Example 4 at page 14 is a patient with metastatic adenocarcinoma who had

failed treatment with taxol, ciplatin and etoposide. The filtration was used to cause tumor inflammation, then followed with thalidomide to cause further tumor regression.

## (6) ISSUES ON APPEAL

The following issues are presented on appeal:

(1) whether claims 1-4, 8, 9, 16, 18-20 and 22 should be rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,708,713 to Lentz;

(2) whether claim 7 should be rejected under 35 U.S.C. § 103(a) as obvious over Lentz in view of Chen, *et al.*, Journal of Neuropathology and Experimental Neurology, pp. 541-550 (May 1997);

(3) whether claim 21 should be rejected under 35 U.S.C. § 103(a) as obvious over Lentz in view of U.S. Patent No. 5,523,096 to Okarma; and

(4) whether claims 5, 6, 10-15, 17 and 23 should be rejected under 35 U.S.C. § 103(a) as obvious over Lentz in view of U.S. Patent No. 5,861,483 to Wolpe.

## (7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (i) Claims 1, 2, 3, 4, 9, 18, 19, and 20, drawn to a method of filtration of blood by removal of components having a molecular weight of 120,000 daltons or less, and device for use therein; (ii) 5, 6, 10, 11, 12, 13, 14, 15, 16, 17, and 23, drawn to the use of filtration and an adjunct therapy such as administration of cytokines, chemotherapy or radiation, and systems or kits for use therein; (iii) 7 and 21, drawn to a method and

system for selective removal of specific cytokine or cellular inhibitors in combination with removal of compounds having a molecular weight of 120,000 or less; and (iv) 8, drawn to the combination of filtration to induce an inflammatory response against a tumor by removal of blood components having a molecular weight of 120,000 or less and vaccination using a tumor antigen vaccine.

The claims require different elements: a filter with a molecular weight cutoff of 120,000 daltons suitable for filtration of blood or plasma, having various configurations and adjunct therapies including the administration of agents to elicit an inflammatory reaction (such as cytokines) or inhibit angiogenesis or induce a specific immune response (vaccine) or selectively remove immune system inhibitors or to kill tumor cells (chemotherapeutic agents and radiation). To make the claimed subject matter obvious, the prior art must disclose the subject matter of each claim as well as provide the motivation to combine as appellant has done.

## (8) ARGUMENTS

### (a) The Invention

The claimed invention is discussed above. This is a method, and a system, for treating patients having a disorder such as cancer. As demonstrated by the examples, tumor remission can be induced by filtration of the patient's blood to remove those molecules having a molecular weight of 120,000 or less. This has a tremendous advantage over the prior art discussed below, because it allows the patient to retain

antibodies to fight disease, which kills many cancer patients. The adjunct therapies are important to induce further remission and maintain remission. The efficacy of this treatment could not be predicted. It was only by actually treating patients that one could determine that the method would be effective.

**(b) Rejections Under 35 U.S.C. § 103**

*(i)* *U.S. Patent No. 4,708,713 to Lentz*

*Lentz does not disclose either a cutoff of 120,000 D nor Adjunct Therapy*

Lentz issued to the appellant based on his initial discoveries many years ago. Lentz discloses using a filter to remove all blood components of 200,000 mw or less to treat cancer patients. While favorable results were obtained, the patient loses all of the IgG and IgA antibodies, which are extremely important to fight infection. Since infection is a major problem for cancer patients, this method would not have been developed if the patentee had believed that one did not have to remove the immunoglobulins. However, it simply had not been determined even as of the issue date of the '713 patent (1987), what component(s) was being removed by the procedure, which allowed the patient to then fight off the cancer.

It has taken years of subsequent work to determine that the "bad" component which is removed by the procedure is a relatively low molecular weight component, allowing the substitution of a filter with a lower molecular weight cutoff.

There is no disclosure of combining filtration with other methods to induce further remission or maintain remission.

*Lentz teaches to remove High Molecular Weight Compounds*

At col. 6, lines 34-46, Lentz specifically states that the **immunosuppressive element** "is believed to be an IgG type immunoglobulin molecule. The other fraction has a molecular weight between about 200,000 and 1,000,000 and is believed to be an immune complex.".

Accordingly, not only is there no disclosure of using a filter with a molecular weight cutoff of 120,000 daltons, there are two specific statements in Lentz **arguing the criticality of the higher molecular weight cutoff of the filter**, teaching away from what appellant has now developed. One skilled in the art would simply not practice the currently claimed method because Lentz teaches that it would **not** be successful!

*The legal standard requires the Prior Art Provide Motivation to Use*

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. ["The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellant's disclosure." M.P.E.P. § 706.02(j) (citing In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991)).

There is absolutely no teaching in the '713 patent that would lead one of skill in the art to believe that a filter having a lower molecular weight cutoff could be used. It is well established that a reference(s) cited under §103 must not only disclose the elements appellant is claiming but the motivation to use them as appellant has done, with an expectation of success.

(ii). *Chen, et al., J. Neuropath. Exper. Neurol. 56(5), 541-550 (1997)*

Chen teaches that soluble TNF-alpha receptors suppress the patients ability to fight cancers. Soluble TNF-alpha receptors are 55,000 and 75,000 daltons in size (page 541, col. 1).

As discussed above, Lentz teaches that something about the size of an immunoglobulin (more than 120,000 daltons), or larger, is instrumental in suppressing a patient's ability to fight a tumor.

Therefore the combination of Lentz with Chen is **not** the same as what appellant is claiming. Moreover, there is nothing that would lead one to believe that only the smaller molecular weight molecules could be removed and the cancer be treated effectively, based on Lentz. Accordingly, one skilled in the art would be led **away** from the combination of Lentz and Chen, **not** to a **modified combination**.

*(iii)* *U.S. patent No. 5,523,096 to Okarma*

Okarma, et al., describes removal of cytokines. Okarma, et al., teaches away from removal of other blood components, stating that removal of the cytokines alone is sufficient to treat the patient.

There is nothing that would lead one to combine Okarma, et al., with Lentz, modify Lentz to remove lower molecular weight blood components (i.e., molecular weights 120,000 daltons or less rather than 200,000 daltons), modify Okarma et al., to

leave in the cytokines but remove the cytokine inhibitors, and have any expectation of success.

*(iv)* *U.S. patent No. 5,861,483 to Wolpe*

Wolpe does not make up for the deficiency of Lentz. Lentz clearly states that there is an immunosuppressive element of a molecular weight similar to that of an immunoglobulin or an immunoglobulin complex which must be removed for a patient to effectively fight the cancer. Wolpe states that certain factors are known which enhance the immune system. Wolpe does not address the issue of whether or not there is an immunosuppressive component having a molecular weight in the critical range between that which is now claimed and that which is taught in the thirteen year old patent to Lentz, prior to many subsequent studies which were required to determine that the immunosuppressive element does **not have a molecular weight similar to that of an immunoglobulin or immunoglobulin complex.** The difference is important: by using the lower molecular weight cutoff, the patient can keep their own immunoglobulin, helping them to more successfully fight off infection.

*(v)* *Any Prima Facie Case of Obviousness Has Been Rebutted.*

For the foregoing reasons, no *prima facie* case of obviousness has been established. Nonetheless, even if a *prima facie* case somehow were established, it would have been rebutted by the appellants' experimental evidence showing that actual cancer patients were treated with the claimed method with dramatic results, patients who had

failed to respond to standard cancer therapies [see Examples 1-4 on p13, line 10 to page 15, line 5].

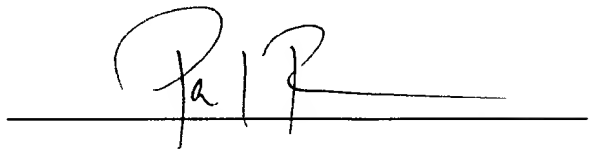
*(vi)* *Appellants' Claims Do Not Stand or Fall Together.*

As noted above, the claims differ in the required elements, as well as the motivation to combine. Group 1 claims the method for inducing an immune response against transformed, infected, or diseased tissue by removing only components present in the blood having a molecular weight of 120,000 daltons or less. Group 2 claims the method of Group 1, but further comprises treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation. Group 3 claims the system or kit similar to that disclosed in Group 1, but further includes selectively removing TNF receptor 1 or TNF receptor 2 molecules, or removing specific cytokine or cellular inhibitors. Group 4 claims the method of Group 1, but further includes vaccinating the patient where the vaccine is produced by immunization with antigens unique to the transformed, infected or diseased tissue. One of ordinary skill in the art would not be led from what is claimed in one of these groups to what is claimed in any of the others. The patentability of these specific groups therefore require a separate analysis.

## (9) SUMMARY AND CONCLUSION

For the foregoing reasons, appellants submit that claims 1-23 are novel and nonobvious over the prior art. Allowance of claims 1-23 is earnestly solicited.

Respectfully submitted,



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**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)**

I hereby certify that this Appeal Brief, together with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: July 12, 2000

## APPENDIX: CLAIMS ON APPEAL

1. A method for inducing an immune response against transformed, infected or diseased tissue comprising

removing only components present in the blood having a molecular weight of 120,000 daltons or less, until the transformed, infected, or diseased tissue is reduced in amount.

2. The method of claim 1 wherein the tissue is a solid tumor.

3. The method of claim 1 wherein the components are removed from one blood volume.

4. The method of claim 1 wherein the components are removed in multiple treatments.

5. The method of claim 1 further comprising treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation.

6. The method of claim 5 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

7. The method of claim 1 further comprising selectively removing soluble TNF receptor 1 and receptor 2 molecules.

8. The method of claim 1 further comprising vaccinating the patient with a vaccine against the transformed, infected or diseased tissue, wherein the vaccine is produced by immunization with antigens unique to the transformed, infected or diseased tissue.

9. A system for inducing an immune response against transformed, infected or diseased tissue comprising

a device for removing only components present in the blood having a molecular weight of 120,000 daltons or less, having inlet and outlet means for connection to a pump and tubing to recirculate the blood of a patient through the device.

10. The kit of claim 17 wherein the agent is an anti-angiogenic compound.

11. The kit of claim 17 wherein the agent is a procoagulant compound.

12. The kit of claim 17 wherein the agent is a cytokine.

13. The kit of claim 12 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

14. The kit of claim 17 wherein the agent is a chemotherapeutic agent.

15. The kit of claim 14 wherein the agent is selected from the group consisting of alkylating agents, doxyrubicin, carboplatinum, cisplatinum, and taxol.

16. The system of claim 9 wherein the system includes means for administering radiation to the tissue.

17. A kit for treatment of a patient to induce an immune response against transformed, infected or diseased tissue comprising:

(a) a device for removing only components present in the blood having a molecular weight of 120,000 daltons or less, and

(b) an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation, in a dosage formulation for treatment of the patient in combination with treatment of the patient with the device to remove blood components having a molecular weight of 120,000 daltons or less.

18. The system of claim 9 wherein the device is a capillary membrane filter with a pore size of between about 0.02 and 0.05 microns.

19. The system of claim 9 wherein the device is a parallel plate filter with a pore size of between about 0.04 and 0.08 microns.

20. The system of claim 9 wherein the device comprises filters with different pore sizes or geometries to provide for staggered removal of materials from the blood.

21. The system of claim 9 wherein the device is an absorbant column selectively removing specific cytokine or cellular inhibitors from the blood.

22. The system of claim 9 wherein the blood is plasma.

23. The kit of claim 17 further comprising anticoagulant to treat the device for removal of components from the blood prior to use.